Evaluate Vantage

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EASD – Lilly blooms with full Jardiance outcomes data

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When Lilly said its major outcomes study had found a cardiovascular benefit with Jardiance things were looking good; the detailed data, however, were stunning. A statistically significant 14% reduction in cardiovascular events and even greater benefit in averting heart-related deaths and all-cause mortality should push the diabetes pill into early treatment lines in high-risk patients.

The results from the Empa-Reg Outcome trial should be enough to carry along the entire SGLT2 class, which includes Johnson & Johnson's Invokana and AstraZeneca's Farxiga. Endocrinologists now await news from the Leader trial of Novo Nordisk's GLP-1 agonist Victoza to see if it can parry Lilly's thrust.

Applause

The Empa-Reg Outcome results revealed at the European Association for the Study of Diabetes sent Lilly shares up 6% yesterday to $89.91. The data were just another part of Lilly's run of good clinical luck this year, following investors' excitement over new findings on its Alzheimer's disease project solenezumab. Shares are up 30% since January 1 (*No letting up in pharma as first-half gains outweigh losses, July 2, 2015*).

Because diabetes drugs are taken so widely, and because patients are at a higher risk of heart attacks, heart failure and strokes because of their disease, all major products must undergo massive trials to rule out any cardiovascular damage. For example, Sanofi's Lyxumia and Merck & Co's Januvia have shown non-inferiority to placebo on cardiovascular endpoints, but could not show that they were better (*ESC – Case builds for Jardiance, August 31, 2015*).

To achieve superiority, therefore, was a huge coup, and the Jardiance data were greeted with applause at the meeting in Stockholm. Patients in the trial had to have been diagnosed with cardiovascular disease, but analysts speculated that physicians would infer a benefit for lower-risk patients.

On the primary endpoint, time to first occurrence of cardiovascular death or non-fatal myocardial infarction or stroke, Lilly and Boehringer Ingelheim's pill scored a hazard ratio of 0.86, significant at $p=0.0382$. On cardiovascular death, hospitalisation for heart failure and all-cause mortality, results were even more impressive, with hazard ratios of 0.62, 0.65 and 0.68.

As the myocardial infarction rate could not be shown to be significantly lower in patients taking Jardiance, the cardiovascular death benefit was chalked up largely to the heart-failure win. The SGLT2 mechanism of action, which causes glucose excretion, creates an osmotic diuresis, which in turn lowers blood pressure; this, in turn, ought to help prevent heart failure complications.

Barely a chink in the armour

It was not a perfect day, however. On stroke, there was a non-significant trend in favour of placebo, although researchers said that was the result of events that occurred more than 30 days after treatment concluded.

Yet the other main safety concern – urinary and genital infections and complications resulting from urinary glucose excretion – looked fairly benign, with rates not appearing to be much higher for Jardiance than for placebo.

Taken in total these data will likely drive a shift toward the SGLT2s and away from classes that so far have failed on the superiority front, in part because guidelines will likely be rewritten in favour of Jardiance. As it is the only one with a proven benefit – trials for Invokana and Farxiga will not read out until 2017 and 2019 respectively – Jardiance stands to benefit most since its sales and marketing effort can start using these data.

Jardiance's strongest competition is probably the older DPP-IVs – such as the biggest seller in diabetes, Januvia – as these are oral and positioned in guidelines as an early add-on to metformin. That said, the injectable GLP-1s also probably stand to lose out.

Unless, that is, Novo can show cardivascular benefit in the Leader trial, which is expected to read out in the next few months. This is by no means a slam-dunk since Lyxumia failed to do so in its study earlier this year.

Victoza has proven to be a resilient franchise for the Danish group – this year outselling the entire SGLT2 class – but this lead could evaporate should Leader fall short.

Study	**Trial ID**
Empa-Reg Outcome	NCT01131676
Leader	NCT01179048

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